

SYNTHETIC METHODS INDEX

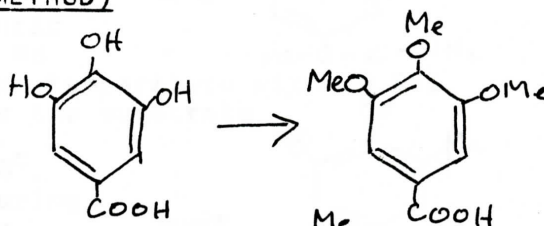
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FROM WORK DONE BY DARRELL LEMAIRE PRIOR TO
OCTOBER 1986.

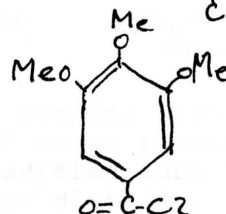
PROCEDURE 9

MESCALINE (SHORT METHOD)

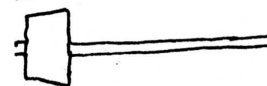
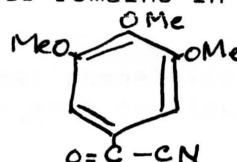
- 9A) Gallic acid is converted to trimethyl gallic acid (3,4,5-trimethoxy benzoic acid) by the procedure in Organic Syntheses, Vol. I, p. 537. 89 - 92% yield M.P. 157 - 160°



- 9B) 100 g. of the dry 3,4,5-trimethoxy benzoic acid is placed in a 1000 ml Erlenmeyer flask and heated to 110° for 20 - 30 minutes in an oil bath of that temperature while under vacuum. This removes any residual moisture. Cool, add 95 g. phosphorus pentachloride and mix by rolling around in the flask. Connect to a distillation apparatus. If the reaction does not start spontaneously, warm the flask a little. Soon a vigorous reaction takes place and some POCl₃ distills over with copious HCl gas being evolved. When the reaction has subsided, distill the remainder of POCl₃ under reduced pressure; water pump is fine. Heat to a pot temperature of 120° and until no more POCl₃ distills over. 3,4,5-trimethoxy benzoylchloride remains in the flask.



- 9C) While the above is going on, dry 300 g. powdered CuCN in a flask in oil bath at 150° under vacuum for 20 minutes, or more. Add the liquid (melted) 3,4,5-trimethoxy benzoylchloride to the hot dried CuCN and mix with a stainless steel paddle until uniform. Stopper with a stopper which has a 6 mm diameter glass tube through it and extending 7 or 8 inches above the stopper. Heat flask in stirred oil bath at 160 - 165° for three hours. Scrape down the neck and sides of the flask occasionally. Scrape out hot product into a covered dish; cool, pulverize and extract with hot heptane; the CuCl₂ and excess CuCN remain insoluble. This is what we used, but other solvents would be better, I'm sure. On cooling, the heptane deposits yellow crystals of 3,4,5-trimethoxy benzoyl nitrile. If it does not have any orange color to it, this is generally pure enough for the next step, but best all around results are obtained by vacuum subliming the benzoyl nitrile in a Kugel Rohr. about 80% yield for steps 9B and 9C.



9D)

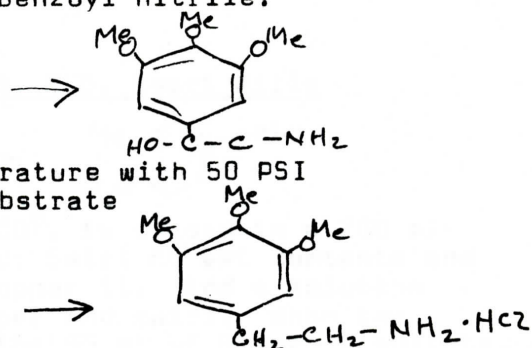
Hydrogenation of the 3,4,5-trimethoxy benzoyl nitrile:

Place 30 g. of the benzoyl nitrile in a glass lined autoclave equipped with stirrer and heater. Add 1200 mL acetic acid, 67.5 g. conc. sulfuric acid, 24 mL water and 15 g. 10% Pd on charcoal. Hydrogenate at room temperature with 50 PSI hydrogen pressure. This reduces the substrate to hydroxy mescaline.

Raise the temperature to 50 - 60°, pressure 50 PSI for 3 hours. During both of these hydrogenations the absorption rate of hydrogen will drop off and stop by the end of the time specified. Cool, filter off catalyst, washing with a little acetic acid. Distill acetic acid off under reduced pressure - a rotovap works well using the addition tube to constantly add more liquid to the flask as it distills. A large amount of liquid in the flask wants to bump badly.

When only a small amount of liquid remains, cool and neutralize with 33% NaOH to a pH of 10. Extract with benzene, dry solvent and remove benzene by distillation, finishing in a rough vacuum. Short-path vacuum distill the residue in a Kugel Rohr. Wash out receiver with a little IPA; and with external ice bath cooling, neutralize the amine with IPA/HCl. When slightly acid, add 2 volumes of t-Bu Me ether and filter. Suction as dry as possible and wash with cold acetone until cake is white and filtrate colorless. 75 - 80% yield from this step.

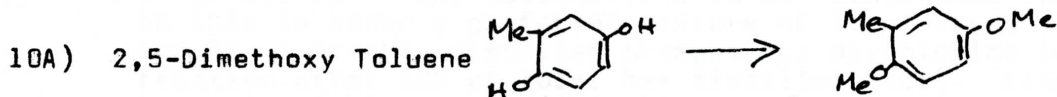
Mescaline hydrochloride M.P. 182 - 184°



This general method could be used to make other phenethylamines if the requisite substituted carboxylic acids were available or easily synthesized.

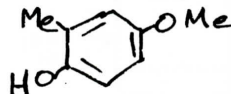
PROCEDURE 10

2,5-Dimethoxy-4-Methyl Phenethylamine, 2CD, MLO, Smart Pills



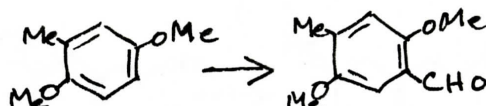
22.5g methyl hydroquinone, m.p. 128-130°, is placed in a 250 ml Erlenmeyer flask and 93 ml water added; Swirl to wet contents and purge with propane or nitrogen and stopper it. Add a solution of 25 g. NaOH in 50 ml water. Restopper and swirl. When the solid has dissolved add about 1/3 of the 35 ml of Dimethyl sulfate, restopper and shake the contents. Cool in external cold water-bath as necessary to moderate temperature so that it is not hot to the touch. Carefully vent any gas pressure build-up with the stopper. When this aliquot has reacted, add the second 1/3 of the dimethyl sulfate and proceed as before. When reacted, add the final 1/3 and do not cool it, as the reaction is slower now and needs the heat to finish. During this time, a light oil will separate and float on top of the reaction mixture. When the final aliquot has reacted, place flask in boiling water-bath or reflux on hot plate for 30 minutes, (replace stopper with reflux condenser). Transfer the hot contents to a separatory funnel and allow the light-colored oil to separate on top of the aqueous phase. Draw off the aqueous portion, reserving it for by-product workup in 10AA. Wash the oil gently with 50 ml hot water, separate, and discard water wash. Dry the oil by filtering through powdered sodium sulfate and purify by Kugel-Rohring (short path vacuum distillation). A clear oil will result which will solidify when refrigerated, and has a m.p. of 22°. Yield 20.8g., 75.4%.

10AA) By-product workup. 4-Methoxy o-cresol



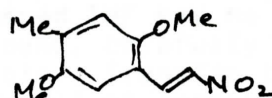
Extract the aqueous with 2 X 25 ml methylene chloride and discard the methylene chloride extract. Make extracted aqueous acid with HCl (pH 1-2) added slowly with stirring; becomes cloudy and a dark oil separates. Extract oil with methylene chloride 3 X 25 ml. Pool extracts and remove solvent by distillation, finish in vacuum. The brown oily product is crude 4-Methoxy o-cresol, which solidifies on standing and can be recrystallized from hexane yielding a purer product which melts at 71-72°. This material can be used to make 2CD5EtO by ethoxylation, Vilsmier synthesis, nitromethane condensation and LAH reduction. See 11A for details.

10B) 2,5-Dimethoxy-4-Methyl Benzaldehyde

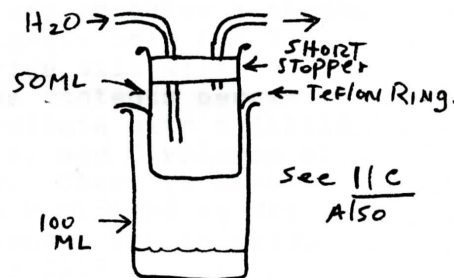


17 g. 2,5-Dimethoxy toluene in a 50 ml roundbottom flask; to this is added a preformed mixture of 10 ml Dimethylformamide and 10 ml freshly distilled phosphorous oxychloride (use middle fraction after 10% of total has distilled over). Attach drying tube with CaCl_2 or Drierite and place in boiling water bath. Swirl frequently to mix phases and then swirl occasionally over three hours at temperature. Pour over 20 g. of crushed ice in a beaker, stir and add more ice if necessary during careful neutralization with 20% NaOH to a pH of 6. Stir very well during neutralization. Filter and wash with water; dry on filter paper on several layers of paper towel or press between filter paper and paper towels. Triturate (grind in mortar and pestle) with a small amount of methyl alcohol (enough to make a creamy slurry) then filter, wash with ice cold MeOH and dry. m.p. $73-74^\circ$.

10C) 2,5-Dimethoxy-4-Methyl Nitrostyrene



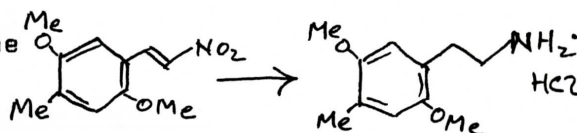
10 g 2,5-Dimethoxy-4-Methyl Benzaldehyde is placed in a 100 ml Berzelius beaker and 10 ml Nitromethane added with 5.4 g. ammonium acetate. Attach a 50 ml beaker condenser (see drawing) and place on pre-heated hot plate; shortly refluxing starts and the reaction is timed from the first drop of reflux. Reflux for 15 minutes and cool quickly by rotating the reaction beaker in a slush of ice and salt. Shortly the melt will solidify to an orange mass. The solid cake is cut up with a spatula into 1/4-inch or smaller squares, and then washed in the beaker with 80 ml of water three times, decanting the wash from the product. This dissolves the ammonium acetate and some of the excess nitromethane from the solid. Dry on a paper towel, patting to remove most of the water. Heat the resulting damp solid with 120 ml ethyl alcohol until it boils gently. Continue heating until all of the orange solid has dissolved and a clear red-orange solution results. ^{Cool} Filter, pressing cake to expel all possible solvent, cut up, and dry in drying oven. m.p. $116-117^\circ$
Lit. m.p. $118-119^\circ$ Yield ~7 g.



* cool overnight in Refrigerator IF POSSIBLE.

This reaction, which occurs many times in the following procedures, should be done with a maximum size of 10 g. of the substrate for best yields and purity of product. Larger batches do not work as well.

10D) 2,5-Dimethoxy-4-Methyl Phenethylamine



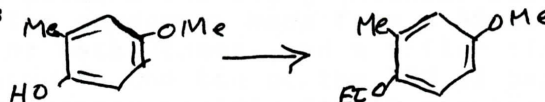
10 g. of the nitrostyrene dissolved in 50 ml warm anhydrous THF is added dropwise to a gently refluxing solution of 6.25 g Lithium aluminum hydride (LAH) in 175 ml anhydrous THF (in 500 ml round bottom flask) over about 30 minutes.

Reflux gently overnight with moisture trap on condenser top. Cool, destroy excess LAH with 33% NaOH dropwise while stirring rapidly. During the NaOH addition, the mixture will get too thick to stir, add THF (washing grade is OK) to thin and continue 33% NaOH addition. When the slurry thins out and settles with a clear supernatant liquid on top, when the stirrer is stopped, the LAH is all destroyed. Add about 30 ml (dry measure) of diatomaceous earth, stir and filter. Wash with washing grade THF and press filter cake to get as much solvent out as practical. Distill the THF using a water bath for heating the flask; the recovered THF may be used for washings. When the THF stops coming over, carefully finish in vacuum to remove as much THF as possible. Transfer the flask and contents to the Kugel-Rohr and distill at less than 2 mm mercury. The product will be a colorless oily liquid which is drained into a 50 ml beaker and the receiving bulb washed into the same beaker with 3 - 5 ml Isopropyl alcohol (IPA). With stirring and external ice cooling, add dropwise a strong solution of dry HCl gas in IPA until slightly acid (pH 2 with external pH paper). The hydrochloride salt will crystallize out part way through, and the contents become very thick. If too thick to stir well, dilute with a little t-Butyl methyl ether. When slightly acid, add 2 volumes of t-Butyl methyl ether, stir and let chill. Check to make sure it is still acid, and filter. When suctioned as dry as possible, wash 2 times with cold acetone. Dry in oven, 80°. Yield about 8 grams. M.P. 210 - 212°

PROCEDURE 11

2 Methoxy-5-Ethoxy-4-Methyl Phenethylamine, 2CD5EtO

- 11A) The by-product from working up the aqueous solution part 10AA is treated thusly:

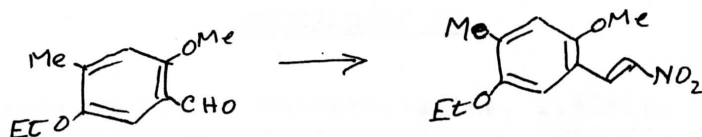


6.2 g powdered KOH is added to 10 ml DMSO in a 50 ml beaker and stirred at room temperature for 5 minutes. Then add 4.1 ml Bromo Ethane followed immediately by 5.5 g of the substrate in 10 ml DMSO. The reaction exotherms some and is stirred for 15 minutes; break up the cake of precipitated KBr as it forms. Pour into 100 ml cold water with stirring; a clear oil separates. Wash oil after separating from the reaction mixture with 100 ml water twice. Extract last water wash and oil with MeCl_2 , dry and remove solvent. Kugel-Rohr the oil. Yield 5.4 g of a water-white oil.



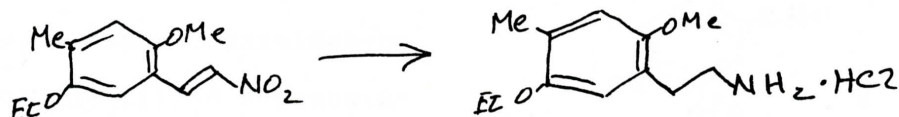
- 11B) 5.25 ml N-Methyl formanilide and 3.29 ml Phosphorus oxychloride (freshly distilled) is incubated at $50^\circ\text{C} \pm 2^\circ$ for 20 minutes. Then add 3.72 g of the substrate from the previous step, attach a Calcium Chloride drying tube and heat in a boiling water bath with frequent swirling for 3 hours. The mixture turns red and HCl gas is evolved slowly. After the heating period, pour over 40 g crushed ice in a beaker and mix with a stirring rod. Add 20% NaOH solution slowly with stirring until the pH is about 6. Filter and wash the cake twice with cold water. Place damp cake on layered paper towels to remove most of the water. Stir the resulting damp solid with 6 ml Methyl alcohol/water (80/20 by volume), breaking up lumps with stirring rod and after 5 minutes stirring, filter, washing with a little of the same Methyl alcohol/water mixture. Let dry at room temperature overnight or until dry. Yield 3 g of a tan powder. M.P. $81 - 82^\circ$

11C)



10 g of the aldehyde from 11 B is placed in a 100 ml tall form beaker with 10 ml Nitro methane and 5.5 g ammonium acetate crystals. A beaker reflux condenser made from a 50 ml beaker, a stopper, and 2 glass or metal tubes, and a teflon ring (see 10C for drawing) is placed in the top of the 100 ml beaker and the mixture refluxed rather rapidly for 15 minutes - time from the first drops from the beaker condenser. Remove from hot plate and cool quickly in a slush of ice/salt/brine, rotating the beaker so that when the reaction mass solidifies, it coats the lower wall of the beaker. When the mass is solid, cut it up with a metal spatula into 1/4 inch or smaller pieces and wash with 80 ml cold water 3 times, decanting the washings through an 80 mesh screen to catch any particles which may tend to float out. Dry on paper towels to damp or dry. Yield crude product 10.5 g. Recrystallize from 200 ml Ethyl alcohol-bring to boiling to dissolve, and cool, then chill and filter. Yield 7.5 g. MP 112.5 - 113.5°

11D)

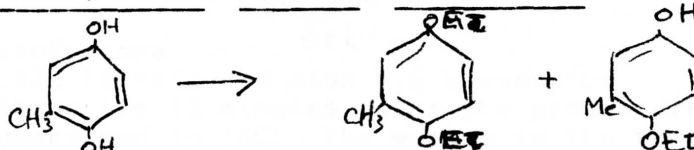


10.4 g. of the Nitrostyrene dissolved in 45 ml warm anhydrous THF is added dropwise over a 30 minute period to a gently refluxing solution of 6.25 g LAH in 175 ml dry THF. When all has been added, attach a moisture trap to the condenser top and reflux overnight. Destroy the excess LAH and work up following the procedure in 10D. The yield of the hydrochloride salt is 6.9 g. M.P. 192 - 194°

PROCEEDURE 12

2,5-Diethoxy-4-Methyl Phenethylamine, 2,5DiEt, Smart Pills

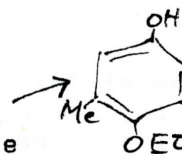
12A) 2,5-Diethoxy Toluene



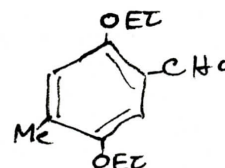
22.5 g Methyl hydroquinone is ethylated with 56 g (47.5 ml) of Diethyl Sulfate using the procedure of 10A except no water cooling is used and a warm water bath (50°) is used instead due to a slower reaction rate.

12AA)

The by-product in this case is 4-Ethoxy o-cresol which is used in making the 2-Ethoxy analogs; see procedure 13 for details. The same procedure is used in recovery and purification as in 10AA.

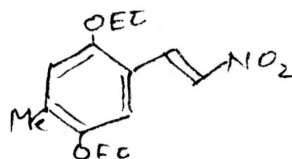


12B) 2,5-Diethoxy-4-Methyl Benzaldehyde



4.5ml freshly distilled Phosphorus Oxychloride and 7.2 ml N-Methyl formanilide is incubated at 50° ± 2° for 20 minutes. Then add 6 g of the substrate, then add a calcium chloride drying tube and heat in a boiling water bath for 2 hours with frequent swirling. Pour the resulting reaction mixture into 75 ml water and crushed ice (50/50) with rapid stirring. Neutralize to a pH 6 with 20% NaOH added dropwise with rapid stirring. When the hydrolysis is complete and the pH stabilized at 6, filter and wash with cold water. The damp, crumbly, brown cake is triturated with just enough cold Methyl alcohol to make a smooth, thin paste. Then filter and wash with cold MeOH and dry in ambient air. Yield 6.2 g of a tan granular powder. M.P. 97 - 100°

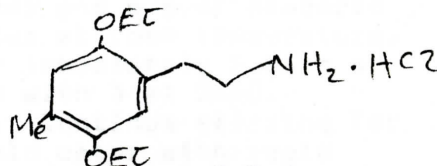
12C)



2,5-Diethoxy-4-Methyl Nitrostyrene

6 g of the aldehyde from 12B is refluxed with 4.5 g Ammonium acetate and 6 ml Nitromethane for 13 minutes using the procedure and beaker condenser as described in 10C. The workup is the same, recrystallizing from 30 ml EtOH. M.P. 107 - 109°

12D)



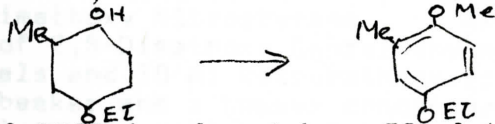
2,5Diethoxy-4-Methyl Phenethylamine

3.6 g of the nitrostyrene in 30 ml warm anhydrous THF is added dropwise over 20 - 30 minutes to a gently refluxing solution of 2 g LAH in 75 ml THF. Reflux overnight. Workup as described previously in 10D. Yield is 2.7 g M.P. 251 - 252°

PROCEEDURE 13

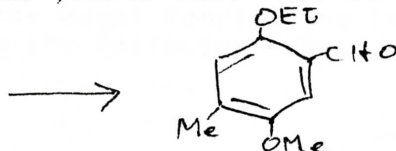
2-Ethoxy-5-Methoxy-4-Methyl Phenethylamine, 2CD2EtO

- 13A) The 4-Ethoxy o-cresol from 12AA is methylated as follows:



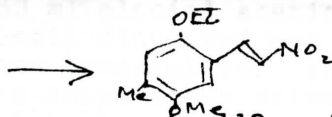
17.6 ml DMSO is placed in a 50 ml beaker and 6 g of powdered KOH added and stirred for 5 - 10 minutes at room temperature. Then add 3.5 ml Methyl Iodide and then immediately 5.64 g of the 4-Ethoxy o-cresol (neat) washed in with 3 ml DMSO. The reaction exotherms to about 80° C. Continue stirring for 15 minutes and pour into 115 ml ice cold water with rapid stirring. An oil separates which is extracted with Methylene Chloride, dried over Na₂SO₄ and solvent removed by distillation, finishing in a vacuum. Kugel Rohr residue. Yield 5.8 g pale yellow oil. This is 2-Ethoxy-5-Methoxy Toluene.

- 13B)



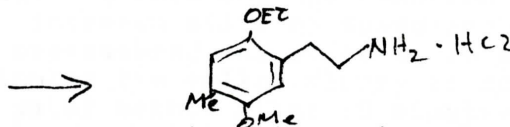
The product from the above step is formylated by the Vilsmier reaction using the same process as 11B. This gives a tan powder. M.P. 59 - 62°

- 13C)



Form the Nitrostyrene the same as in 11C and recrystallize each gram of crude product from 17 ml EtOH. M.P. 107 - 108°

- 13D)

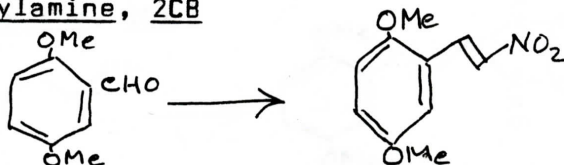


Reduce the above Nitrostyrene with LAH as in procedure 11D. M.P. 207 - 208°

PROCEDURE 14

2,5-Dimethoxy-4-Bromo Phenethylamine, 2CB

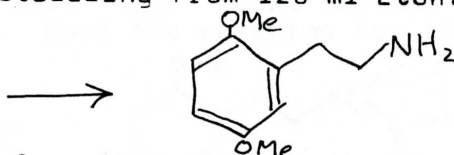
14A)



2,5-Dimethoxy Nitrostyrene

10 g of 2,5-Dimethoxy Benzaldehyde, 5.5 g Ammonium Acetate crystals and 10 ml Nitromethane are placed in a 100 ml tall form beaker and a beaker condenser added. Place on preheated hot plate and reflux rapidly for 10 minutes. Cool and work up as in procedure 10C, recrystallizing from 120 ml EtOH. Yield 8.7 g M.P. 114 - 116°

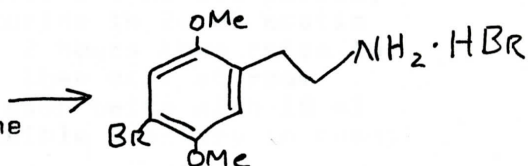
14B)



2,5-Dimethoxy Phenethylamine

The 2,5-Dimethoxy Nitrostyrene from the previous step is reduced with LAH using the procedure in 10D with proportional amounts of reagents depending on the batch size. Stop the procedure after Kugel Rohring the free amine and use this oily liquid in the following step.

14C)



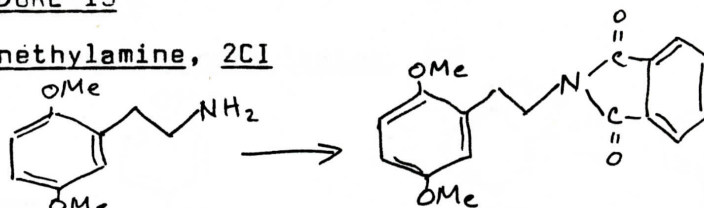
2,5-Dimethoxy-4-Bromo Phenethylamine

10 g of the 2,5-Dimethoxy Phenethylamine from 14B is added slowly with stirring to 30 ml glacial acetic acid in a 100 ml tall form beaker. Stir until dissolved and the resulting solution has cooled to room temperature. Then add, with stirring, (strong variable-speed motor drive with broad stirring blade; a stir bar is too weak!) over a one-half minute period, 9.65 g of Bromine in 10 ml acetic acid. Soon crystals will begin to form and the reaction mixture becomes quite thick; Increase stirring speed and add 15 ml acetic acid which is premeasured and at hand, to thin the mixture. After 15 minutes the yellow slurry is cooled externally with cold water bath. After 10 minutes, ice is added to the water bath to cool further. Keep the bath temperature above 6° or the acetic acid will freeze. Stir 15 minutes. Filter, washing stirring blade and beaker out with a few ml (10 ml) cold acetic acid, and use this washing as a first wash for the filter cake. Suction as dry as possible, pressing the cake of fine crystals with the flattened end of a heavy stirring rod. Wash cake with chilled acetone (6° - 8°) until the cake is white and the washings colorless. Dry cake in a 60° oven until no acetone odor is present. This is the Hydrobromide salt of 2CB and is very water soluble, and is ready for use. Yield 16.2 g M.P. 212 - 214°

PROCEDURE 15

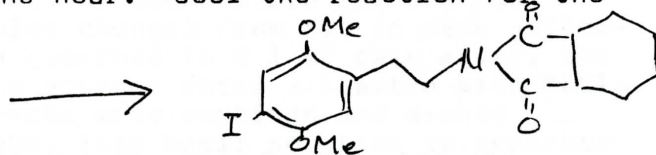
2,5-Dimethoxy-4-Iodo Phenethylamine, 2CI

5A)



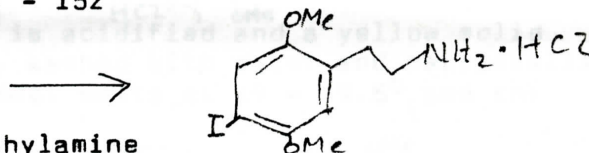
2,5-Dimethoxy Phenethylamine is prepared as in steps 14 A & B. 13.3 g of this amine is reacted with an equimolar quantity of phthalic anhydride (10.86 g) in a 100 ml Berzelius beaker heated in an oil bath maintained at $150^{\circ} \pm 2^{\circ}$. This is to protect the amine group in the next step. Total heating time for this reaction was one hour. Cool the reaction for the next step.

15B)



The phthalimide from step 15A is dissolved in 120 ml acetic acid with warming and then cool to room temperature. Then add to the stirred solution, over a 4 minute period, a solution of 12.2 g Iodine Monochloride in 28 ml acetic acid. Stir at room temperature for 2 hours then raise the temperature to 60° for 30 minutes. Then stir at room temperature overnight. Filter and wash twice with 10 ml acetic acid. Suction as dry as possible then dry in oven. Yield 16.75 g M.P. $151 - 152^{\circ}$

15C)



2,5-Dimethoxy-4-Iodo Phenethylamine

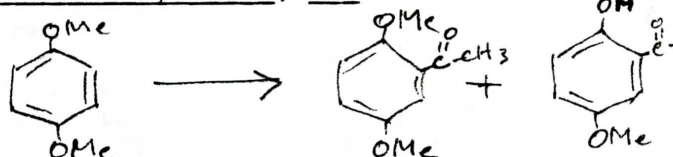
16.7 g of the phthalimide from 15B is placed in a 500 ml round bottom flask and 103 ml of 95% ethanol and 30 ml of 100% ethanol are added. Add 2.65 ml 85% Hydrazine Hydrate and boiling chips- reflux for 22 - 24 hours. Cool to room temperature and filter off the white solid. Yield 17.18 g M.P. $214 - 233^{\circ}$

Place the dried white solid in a 400 ml beaker and add 75 ml 20% NaOH, warm with occasional stirring - soon all is dissolved and a heavy oil separates. Transfer to separatory funnel and draw off heavy oil; extract the aqueous with 20 ml MeCl_2 twice. Dry MeCl_2 extract through Na_2SO_4 and remove solvent. Combine the residue from MeCl_2 extraction with the heavy oil drawn off previously. A little IPA may be used to rinse all of the oily product into the other beaker. Then with external ice cooling, neutralize the amine with IPA/HCl until slightly acid to external pH paper. During this time, the product will crystallize out. Add two volumes of t-Butyl Methyl Ether, stir and check to make certain it is still acid - add more IPA/HCl if necessary. Filter, suction as dry as possible, and wash with acetone until the cake is white and the filtrate colorless. Dry in oven. Yield 11.3 g M.P. $250 - 252^{\circ}$

PROCEDURE 16

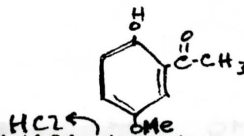
2,5-Dimethoxy-4-Ethyl Phenethylamine, 2CE

16A) 2,5-Dimethoxy Aceto Phenone



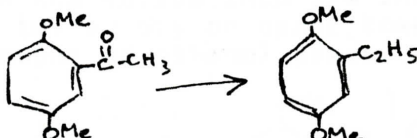
To a suspension of 116 g of anhydrous AlCl_3 in 350 ml MeCl_2 was added with stirring 0.8 mole of acetyl chloride. This mixture was added slowly and with vigorous stirring to a solution of 92 g p-dimethoxy benzene in 300 ml MeCl_2 . This was allowed to stir at ambient temperature for one hour during which time the color changed from red to dark yellow-green. The reaction was quenched in 2 l of cold water, the phases separated, and the aqueous phase extracted with MeCl_2 twice. The organic extracts were combined and washed several times with 5% NaOH ; this basic solution is reserved for by-product work up under 16AA. The organic extracts are then washed with dilute HCl once and the solvent removed by distillation, finishing in a vacuum. The product is then Kugel Rohred to yield a colorless oil. Yield about 75%

16AA) 2-Hydroxy-5-Methoxy Acetophenone



The basic solution from 16A is acidified and a yellow solid separates which is filtered, washed with water and recrystallized from hot methanol. The product melts at $49 - 49.5^\circ$ and the yield is about 15%.

16B) 1-Ethyl-2,5-Dimethoxy Benzene



To a mixture of 100 g of 2,5-Dimethoxy Acetophenone and 70.5 g of KOH in 500 ml of triethylene glycol is added 80 ml of 85% hydrazine hydrate. The mixture is refluxed for 4 hours with removal of water by distillation allowing the pot temperature to reach 190°C , and then reflux for another one hour. The cooled reaction mixture and the aqueous distillate which contains some codistilled product are combined, diluted with 1 l water and extracted 5 times with 100 ml MeCl_2 . The combined organic fractions are dried, filtered and distilled to yield an oil which is then Kugel Rohred to give 73 grams of a colorless oil. B.P. $104 - 105^\circ \text{C}$ @ 7 mm.

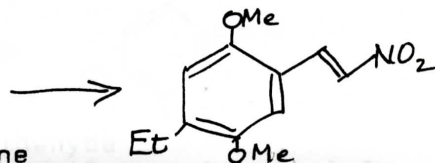
16C)

**2,5-Dimethoxy-4-Ethyl Benzaldehyde**

5.25 mL N-Methyl formanilide and 3.3 ml freshly distilled POCl_3 is incubated at 50° for 20 minutes; then add 3.2 g. of the substrate, attach a CaCl_2 drying tube and heat in a 90° water bath with frequent swirling for 15 - 20 minutes. HCl gas is gently evolved during this time. Cool, pour into 20 ml water and 20 g. crushed ice. Stir while adding 20% NaOH dropwise to neutralize the reaction mixture. When the pH is 6, filter the solids and wash with water. Dry on paper towel. Triturate with 10 ml $\text{MeOH}/\text{H}_2\text{O}$ (80/20 by volume), filter and wash with $\text{MeOH}/\text{H}_2\text{O}$. Dry in air overnight. M.P. $45 - 46^\circ$, tan powder - yield varies.

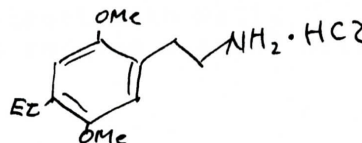
The reaction progress could be followed by TLC but the results would be useful only for the next preparation, since the reaction time is short. Another approach would be to use the procedure in 10B, which uses dimethyl formamide instead of the more reactive N-methyl formanilide. Here, TLC would be more useful due to a longer reaction time. A lower temperature (90°) may be more favorable also, for better yields and less tar formation.

16D)

**2,5-Dimethoxy-4-Ethyl Nitrostyrene**

5 g. of the aldehyde from 16C, 2.5 g. ammonium acetate and 5 ml nitromethane are refluxed in a beaker with a beaker-condenser for 15 minutes. Cool the reaction mixture in an external ice/brine slush, cut up the solids into 1/4 inch or smaller pieces, wash with water twice, dry on paper towel. Recrystallize from the minimum amount of ethanol practical. MP. $97 - 98^\circ$ Yield 80%

16E)

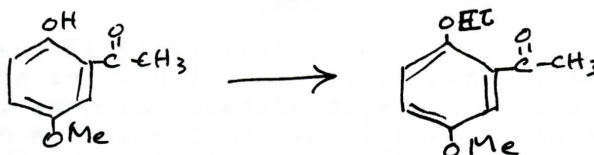
**2,5-Dimethoxy-4-Ethyl Phenethylamine**

The nitrostyrene from step 16D is reduced to the amine with LAH in THF as described in procedure 10D. M.P. $203 - 204^\circ$

PROCEDURE 17

5-Ethoxy-2-Methoxy-4-Ethyl Phenethylamine, 2CE 5EtO

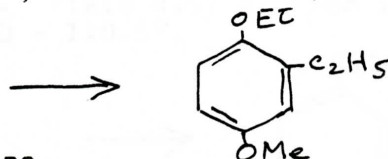
7A)



2-Ethoxy-5-Methoxy Acetophenone

The by-product from 16AA is ethylated following the same procedure as in 11A using proportionally more or less reactants, as available. The yield is about 90% and the M.P. is 32 - 34°.

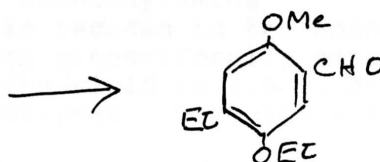
7B)



2-Ethoxy-5-Methoxy Ethylbenzene

The product from 17A is reduced to the ethylbenzene compound using the same procedure as in 16B resulting in a pale yellow oil. Yield about 80%.

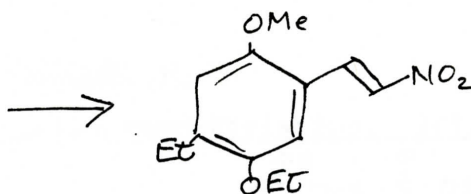
7C)



5-Ethoxy-2-Methoxy-4-Ethyl Benzaldehyde

12.2 mL POCl₃ freshly distilled and 12.8 mL N-methyl formanilide incubated at 50° for 20 minutes, then add 11.1 g. of the product from 17B. Attach a CaCl₂ drying tube and the mixture is heated with swirling over a 10 minute period to the boiling point of the water bath. Heated in boiling water bath for 20 minutes, then poured into 250 mL water and crushed ice with stirring. After a few minutes of stirring, the orange oil became semi-solid. Neutralize to a pH of 6 with 20% NaOH. Extract with MeCl₂, 2 X 30 mL; evaporate solvent. The product remains a thick oil.

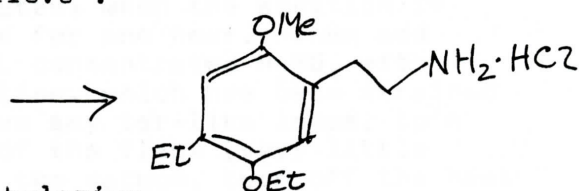
17D)



5-Ethoxy-2-Methoxy-4-Ethyl Nitrostyrene

To each gram of the thick oil from 17C is added 1 mL nitromethane and 0.5 g. ammonium acetate crystals in a small beaker fitted with a beaker condenser. Reflux vigorously for 20 minutes and pour into ice water (20 mL for each gram of substrate) with stirring. Decant most of the water, wash once more with water and decant. Add EtOH (2 mL for each gram of substrate), stir well and filter. Wash cake with small amount of EtOH and dry. Yield 4.97 g. from 10 g. of impure substrate. M.P. 110.0 - 110.5°.

17E)



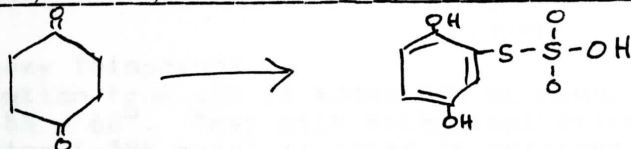
5-Ethoxy-2-Methoxy-4-Ethyl Phenethylamine

The nitrostyrene from 17D is reduced to the amine and worked up as described in 10D using proportionally more or less quantities of reactants. The yield is 1.5 g. of the HCl salt for each 2 g. of the nitrostyrene. M.P. 184 - 185°.

PROCEDURE 18

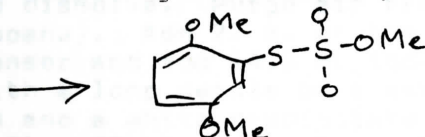
2,5-Dimethoxy-4-Ethylthio Phenethylamine, 2CT2

8A)



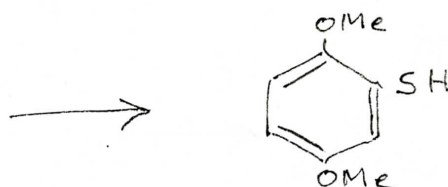
Dissolve 372.5 g. sodium thiosulfate pentahydrate ($\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$) (1.5 mole) in 200 mL warm water and warm further to dissolve, then cool to room temperature. Then with rapid stirring and cooling, (external ice bath or cold water through a stainless steel coil immersed in the reaction) add in a fairly steady stream to the vortex a hot solution of 108.9. (1 mole) p-benzoquinone dissolved in 110 mL acetic acid. The addition should take 10 to 15 minutes; when the addition is complete, stir at room temperature for one hour. Then add slowly over about 5 minutes, 56 mL concentrated H_2SO_4 with rapid stirring. Rotovap the solution, which has been strained through an 80 mesh screen to remove any tar-like lumps, to a solid or semi-solid on the walls of the flask (very little condensate at this point). Break the vacuum, turn off the heat to the water bath and add 700 mL MeOH. Rotate to dissolve, transfer to a large beaker and let stand overnight. Add a dry volume of 100 mL of diatomaceous earth, stir and filter, washing filter cake with MeOH until the filtrate is clear. This results in about 1000 mL filtrate, including washings. Rotovap to about one-half volume, and take to the next step. If it stands for awhile (overnight) it will be a semi-solid and warming will liquify it.

18B)



Place the solution from 18A in a methylating apparatus; the total volume here should be 450 - 475 mL. Add 330 mL dimethyl sulfate, begin stirring and cooling water through the internal cooling coil. Add 360 mL total of 33% NaOH solution in a thin stream of the addition funnel. The temperature goes up - regulate the steady addition of NaOH solution to keep the temperature in the 40 - 45° range. The addition will take 15 to 20 minutes; when all in, turn off cooling water. Check the pH - if it is less than 8, add 10 to 20 mL 33% NaOH solution. Check pH every 5 minutes or less and keep pH above 8 with small (10 mL) additions of NaOH solution. Some gas evolution will occur during this time of stirring. After one hour of stirring, transfer to a wide mouth 5 L Erlenmeyer flask or a 4L beaker for the next step.

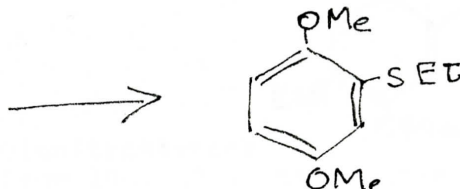
3C)



2,5-Dimethoxy Thiophenol

To the solution from 18B is added 800 mL conc. HCl and warmed to 55 - 60°. Then with mechanical stirring, 460 g. powdered zinc (-325 mesh) is added in portions over a one hour period. Hydrogen sulfide is evolved so the reaction must be done in a hood. Continue heating and stirring until the solution is a clear greenish color. Considerable zinc is unreacted and is in flocculent clumps. Decant the solution from the zinc, then filter the zinc, washing with MeCl₂ to remove any product adhering to the zinc. Dilute the decanted liquid with enough cold water so that there is a good separation of the MeCl₂. Then extract the cold solution (decanted liquid plus filtrate) several times with MeCl₂. The extracts are washed once quickly with 5% NaHCO₃, dried and the solvent distilled, leaving a yellow oil which is vacuum distilled in the Kugel-Rohr. Yield 93.5 g. of a pale yellow oil. with a mercaptan odor.

8D)

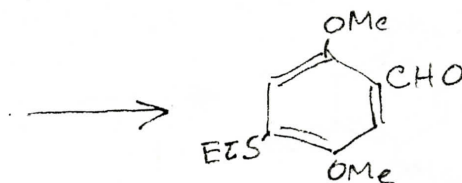


2,5-Dimethoxy Phenylthioether

To 100 mL absolute EtOH is added 10 g. powdered KOH. Stopper and swirl to dissolve. Purge air from flask with an inert gas (N₂, propane). Add 22 g. of the thiophenol from 18C, attach condenser and add 14.0 mL iodoethane through the condenser with a long needle on a syringe. The reaction becomes warm and a white precipitate forms (KI). Add boiling chips and reflux 30 minutes. Cool, filter, and rotovap to a whitish slurry. Transfer flask and contents to Kugel Rohr and vacuum distill the thioether from the KI which remained in solution from the filtering step. Yield about 24 g. of a slightly cloudy, oily, colorless, nearly odorless liquid.

The solution is
little of the
five minutes.
dry the resulting

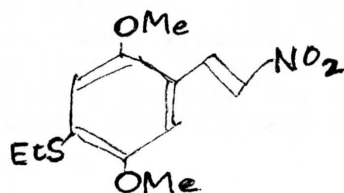
BE)



2,5-Dimethoxy-4-Ethylthiobenzaldehyde

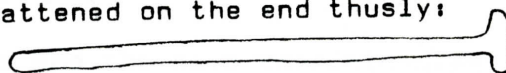
25.5 mL freshly distilled POCl_3 and 35.8 mL N-methyl formanilide is incubated at 50° for 20 minutes. Then add 23.7 g. of the thioether slowly with gentle mixing - slightly exothermic and turns dark red. Attach CaCl_2 moisture trap and place in water bath at 65° . Heat the water bath to boiling over about 10 minutes while swirling the flask contents frequently. Heat at boiling bath temperature for 20 minutes. Cool somewhat and pour into 500 mL ice water and crushed ice with stirring. Stir for 20 minutes - the red oil hydrolyzes to a granular orange precipitate. Filter, wash cake with water, suction as dry as possible and triturate the damp cake with 40 mL ice cold EtOH. Filter, washing sparingly with more ice cold EtOH. Dry in air overnight. Yield 13.5 g. M.P. $85 - 86^\circ$

BF)



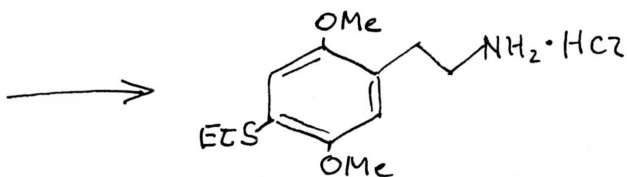
2,5-Dimethoxy-4-Ethylthionitrostyrene

10 g. of the aldehyde from 18E, 10 mL nitromethane and 4.5 g. ammonium acetate crystals are placed in a 100 mL berzelius beaker and a beaker condenser added, and refluxed briskly on a preheated hot plate for 12 minutes. Cool in external ice/salt slush. When solid, cut into 1/4 inch or smaller pieces and wash twice with 80 mL cold water, straining the decanted water through an 80 mesh or finer screen. Air dry overnight, and triturate with 100 mL boiling EtOH in a beaker on a hot plate, grinding the lumps to a fine crystalline powder with the flattened end of a heavy 1/4" to 3/8" diameter stirring rod which has been heated and flattened on the end thusly:



The solution will be bright fluorescent orange-red and very little of the product dissolves, but the impurities do. After five minutes, cover with a watch glass and cool. Filter and dry the resulting fine crystals. Yield 10.7 g. M.P. 146°

18G)



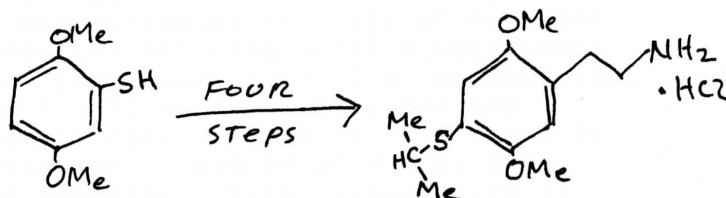
2,5-Dimethoxy-4-Ethylthio Phenethylamine

3.0 g. of the nitrostyrene from 18F dissolved in 35 mL simmering dry THF is added dropwise over a 30 minute period to a gently refluxing suspension of 1.9 g. LAH in 53 mL dry THF. Reflux gently overnight. Cool, add slowly 60 drops 33% NaOH with vigorous stirring, carefully thinning with wash grade THF as needed to maintain a stirable consistency. Add diatomaceous earth and filter, washing the cake with wash grade THF. Remove solvent by distillation, finishing in a vacuum. Transfer the flask containing the yellow oil to the Kugel Rohr and vacuum distill. The nearly colorless oil is drained into a small beaker, washing out the receiver bulb with a small amount of IPA. Then with external ice cooling, a strong solution of dry HCl gas in IPA is added dropwise while stirring. Add more IPA to thin part way through, if necessary. When slightly acid to external pH paper, dilute with t-Bu Me Ether. Stir and filter, washing out beaker with more t-Bu Me Ether. Suction dry and wash with cold acetone until cake is white and filtrate colorless. Dry in 60° oven. Yield 2.2 g. M.P. 199°

PROCEDURE 19

2,5-Dimethoxy-4-Isopropyl Phenethylamine, 2CT4

19A)



The thiophenol from 18C is reacted with 2-iodo propane instead of iodo ethane using the same

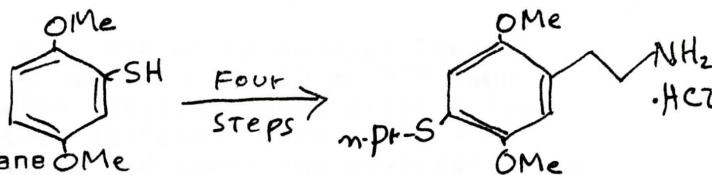
molar quantities of reactants and the same conditions as in 18D. The resulting isopropyl thioether is then taken through steps 18E, 18F, and 18G. The resulting product is the hydrochloride salt of 2CT4. M.P. 195 -196°

PROCEDURE 20

2,5-Dimethoxy-4-n Propylthio Phenethylamine, 2TC7

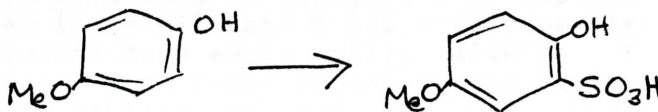
D)

The thiophenol from 18C is reacted with n-iodopropane using the same molar quantities of reactants and the same conditions as in 18D. The resulting n-propylthioether is then taken through steps 18E, 18F, and 18G. The resulting product is the hydrochloride salt of 2CT7. M.P. 191 - 192°



PROCEDURE 21

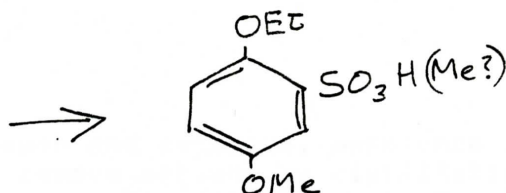
5-Ethoxy-2-Methoxy-4-Ethylthio Phenethylamine, 2CT2-5EtO



21A)

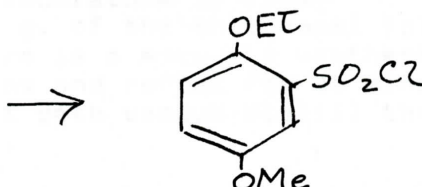
2-Hydroxy-5-Methoxy Phenyl Sulfonic Acid
20 g. of p-methoxy phenol and 12.9 mL 100% sulfuric acid are mixed at room temperature and placed in a 30° water bath and stirred. The temperature was raised at the rate of not more than 1° per minute with constant stirring until a bath temperature of 80° is reached. Cool, pour over 70 g. crushed ice, washing the flask out with 5 - 10 mL H₂O. Stir and add slowly 33% NaOH until slightly basic. The mixture turns to a cottage cheese like consistency. Add 50 mL H₂O to thin and 10 mL more of the NaOH solution. Final temperature is 20° and the volume about 180 mL.

1B)



Transfer the above mixture to a 500 mL Erlenmeyer flask washing out beaker with 15 mL water. Add 10 mL 33% NaOH and 10 mL Diethyl Sulfate with swirling, then after a few minutes, another 10 mL Diethyl Sulfate. Warm to 60 - 65° with swirling to dissolve lumps and speed the reaction. The pH should be kept above 10 - if it drops below, add 10 mL NaOH solution. Add 10 mL diethyl sulfate, continue warming and swirling a few minutes, then 10 mL more diethyl sulfate for a total of 40 mL. Heat on steam bath for one hour.

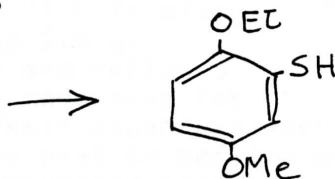
21C)



2-Ethoxy-5-Methoxy Phenyl Sulfonyl Chloride

The solution from 21 B is rotovaped to dryness, then heating of the flask is continued in an oil bath @ 125 - 130° or air bath @ 150 - 160° (Kugel-Rohr oven works well), with an occasional brief air sweep. When fumes appear in the flask during the air sweep, stop heating and cool the flask. Add 75 mL POCl₃ to the foamy crust in the flask. Add reflux condenser and heat in boiling water bath - HCl gas is evolved. After about 20 minutes, most of the crust is broken up with a thin, flat, stainless steel tool. Swirl occasionally as heating continues. At about 1.5 hrs., the entire mass sets up to a semi-solid. Cool and break up semi-hard solids and add to crushed ice with stirring; more crushed ice is added as the hydrolysis continues. Wash out flask with some of the cold aqueous from the hydrolysis. When the hydrolysis is complete, filter and wash the sulfonyl chloride with ice water. Yield about 24 g.

21D)



2-Ethoxy-5-Methoxy Thiophenol

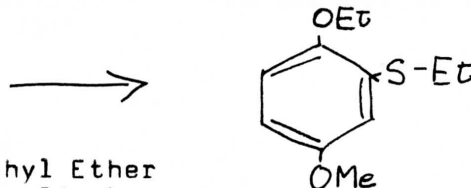
24 g. of the damp sulfonyl chloride from 21 C is added to a mixture of 35 mL conc. sulfuric acid and 560 g. crushed ice.

- 31 g. Zinc powder (-325 mesh) is added with stirring. Attach condenser and mechanical stirrer, place on hot plate and heat to reflux. Reflux with stirring for 1.5 hours. Cool, decant from unreacted zinc and filter the zinc, washing with MeCl₂ to remove any product. Combine the decant and filtrate and extract with MeCl₂.

21D continued)

Dry the combined MeCl_2 wash and extracts, wash once quickly with 5% NaHCO_3 , dry and remove solvent by distillation, finishing in a rough vacuum. Transfer flask to Kugel Rohr and vacuum distill. Yield 7.8 g. of a pale yellow oil.

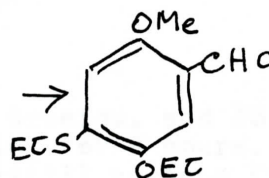
21E)



2-Ethoxy-5-Methoxy Phenyl Thioethyl Ether

To 1.28 g. powdered KOH dissolved in 24 mL absolute EtOH at room temperature is added in sequence quickly 2.5 g. of the thiophenol followed by 2.0 mL of iodo ethane. There is a moderate exotherm and precipitate of KI. Add boiling chips and reflux for 30 minutes, filter, remove solvent and short path vacuum distill the oil. Yield 2.74 g. clear oil.

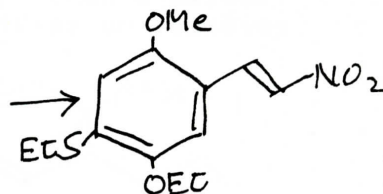
21F)



2-Methoxy-5-Ethoxy-4-Ethylthio Benzaldehyde

10.3 g. POCl_3 freshly distilled and 14.5 mL N-Methyl Formanilide incubated at 50° for 20 minutes. Add 7.5 g. of the thioether from 21 E, add CaCl_2 drying tube, place in a warm water bath and heat the bath to boiling over a 10 - 15 minute period with frequent swirling of the flask contents. After 20 minutes of heating, pour into 150 mL ice/water slush with stirring. Stir for 30 minutes or until until the original thick orange oil has hydrolysed to a granular floc. Filter, wash with water and triturate with methyl alcohol/water (80/20 by volume), filter, washing with a little more of the MeOH/water mixture, dry. M.P. 49° .

21G)



5-Ethoxy-2-Methoxy-4-Ethylthio Nitrostyrene

5 g. of the aldehyde from 21 F is mixed with 5 mL nitromethane and 2.5 g. ammonium acetate crystals and refluxed in a beaker with a beaker condenser for 15 minutes. Cool in ice/salt slush and wash with water twice; drain. Add 30 mL EtOH and heat to boiling with stirring; not all may dissolve. Cool; crystals form shortly; filter and dry. Yield 4.5 g. M.P. $107 - 108^\circ$

1H)

2CT2-5EtO

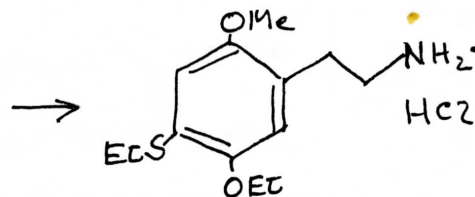
The nitrostyrene from 21G

is reduced to the amine with

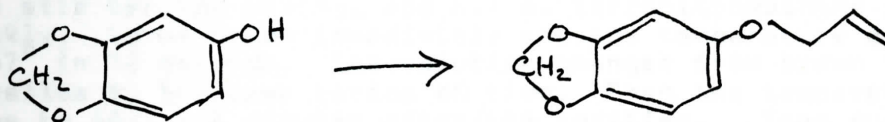
LAH in THF using the procedure

in 18G with proportional amounts

of reactants for the substrates available. The product is 2CT2-5EtO as the hydrochloride salt. M.P. 180°

PROCEDURE 222-Methoxy-4,5-Methylenedioxy Amphetamine, MMDA-2

2A)

3,4-Methylenedioxy Phenyl Allyl Ether

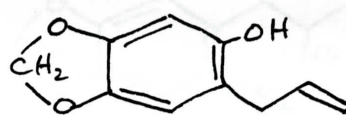
20 g. sesamole, 400 mL acetone, 48 g. allyl bromide, and 80 g. potassium carbonate are refluxed with stirring for 8 hours.

Cool, filter, washing cake with acetone. Distill acetone from the filtrate and washings, finishing in rough vacuum. Clear yellow oil.

2B)

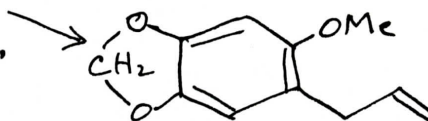
The flask and contents from 22A are heated (air condenser) in an oil bath to about 210°, when a spontaneous exothermic reaction sets in. The temperature rises to about 248° then subsides.

Maintain @ 220° for 5 minutes, cool. Solidifies on standing. Tan solid. M.P. 66 - 68°



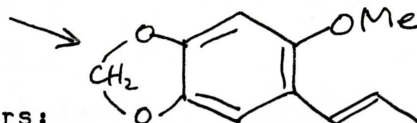
2C)

22 g. of the substrate from 22B, 20 mL MeOH and 20 mL dimethyl sulfate are mixed in a 500 mL flask. Add slowly with mixing

a solution of 14 g. KOH in 30 mL water - connect reflux condenser; mixture becomes warm and boils a little. After a few minutes, add 10 g. KOH pellets through the condenser with swirling. Place on steam bath for 30 minutes, swirl frequently. To the thin tan slurry, is added water to a total volume of 250 mL. A tan oil settles to the bottom. Extract 3 X with MeCl₂. Dry solvent; distill off MeCl₂, finishing in rough vacuum.² Then short path vacuum distill. Yield 21 g. of nearly colorless oil.

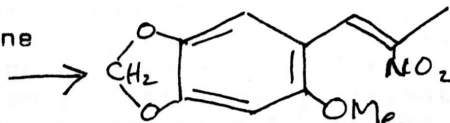
22D)

Reflux the 21 g. of oil from 22C with powdered KOH from 8 pellets at 18 - 20 mm pressure for 2 hours; an air condenser is best. It is usually necessary to make an intentional leak in the vacuum system to get a "poorer" vacuum of 18 - 20 mm pressure. This regulates the temperature and if a "better" vacuum is used (2mm) then refluxing would be necessary for 8-10 hours. Transfer the flask to Kugel Rohr for vacuum distillation. Yield about 20 g. M.P. 45 - 50°



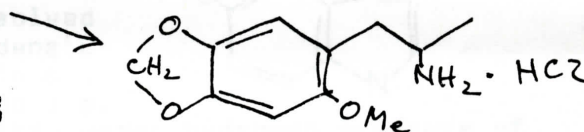
22E)

A solution of 6.2 g. of the propene dissolved in 30 mL acetone and 3 mL pyridine is cooled in an external ice/salt bath to -5°. With stir bar for mixing, add 6.7 g. tetranitromethane rather quickly. Turns brown immediately and the temperature goes up to 37° in 30 seconds. The solution changes from brown to tan to yellow in the same period of time. Then the temperature drops to 10° 2.5 minutes after the addition. Then quench with a prechilled (-50) solution of 2.1 g. KOH in 37 mL water. There is an immediate formation of a yellow slurry too thick for the stir bar - use thermometer instead. At 5°, discontinue stirring and filter, wash with water 2 X, press cake to expel water and dry in air overnight. M.P. of crude is 159 - 161° LIT. M.P. 163° Yield 8.5 g.



22F)

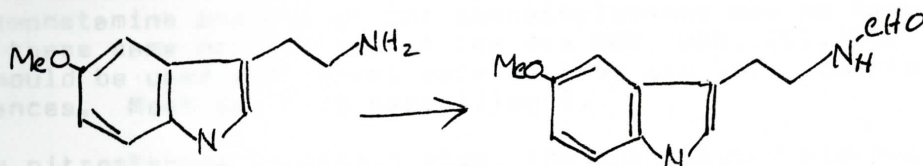
MMDA-2
The nitrostyrene from 22E is reduced with LAH in THF following the same procedure as in 10D. M.P. 185 - 186° LIT. M.P. 187°



PROCEDURE 23

5-Methoxy-N-Methyl-N-Isopropyl Tryptamine, 5MeO-MIPT

3A)

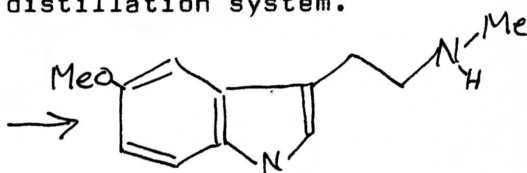


5 g. of 5-Methoxy tryptamine is dissolved in 200 mL methyl formate and heated in a stainless steel autoclave in a boiling water bath with occasional swirling for 2.5 hours. The internal pressure was 105 PSI. Cool, distill methyl formate from the product, keeping the temperature below 40° at the end by reducing the pressure of the distillation system. Yield is nearly quantitative 5.7 g.

23B)

To a stirred suspension of 2.5 g. LAH in 100 mL THF is added dropwise a solution of 5.7 g. of the product from 23A dissolved in 60 mL THF.

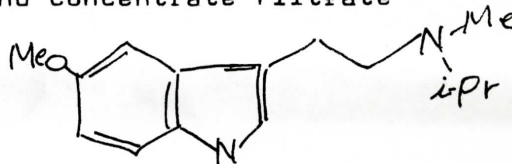
Reflux 30 minutes and cool. Add 50% aqueous THF carefully in sufficient quantity to destroy excess LAH with stirring and external ice bath cooling. Filter and concentrate filtrate under reduced pressure.



23C)

The residue from 23B is dissolved in 120 mL EtOH (grain, not denatured) 2.5 mL acetone placed in a Parr bottle with stir bar and 1 g.

10% Pd on charcoal added. Stir under hydrogen pressure of 50 PSI for 15 hours or more, until the reduction is complete. If some of the 2° amine is unreduced, this causes difficulties in recrystallizing the 3° amine base from ether/hexane. The reduction progress can be followed by TLC. When complete the catalyst is removed by filtration and washing with a few mL EtOH. The alcohol solution as is may be used by measuring the dosage in drops of it to contain so many Mg and placing it in some beverage (fruit juices work well). Dosage 5 - 10 mg. An alternate method is to remove the EtOH under reduced pressure and recrystallize the amine base from ether/hexane. A tan powder results. about 90% yield.



PROCEDURE 24

MISCELLANEOUS

Many amphetamine analogs of the phenethylamines may be made using these same procedures. A few are DOM, DOB, DOI, DOET - and should be used with great care as they are very powerful substances. Most are also very illegal.

In the nitrostyrene formation step, the substituted aldehyde is reacted with nitroethane instead of nitromethane under the same conditions. This gives a 3 carbon side chain which, on reduction, gives the corresponding amphetamine.

